UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,032	12/02/2003	Daniel S. Kohane		4419

7590 07/31/2009

DANIEL S. KOHANE
41 LESLIE ROAD
EWTON, MA 02459

EXAMINER	
HOLT, ANDRIAE M	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
07/31/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,032	KOHANE ET AL.	
	Examiner	Art Unit	
	Andriae M. Holt	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-42 and 44-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-42 and 44-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicant's amendments filed April 13, 2009. Claims 35-42 and 44-58 are pending. Claim 35 has been amended. Claims 56-58 are newly added. Claims 35-42 and 44-58 will presently be examined to the extent they read on the elected subject matter of record.

Status of the Claims

Rejections not reiterated from the previous Office Action are hereby withdrawn. The following rejections are newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-42 and 44-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition for "treating" cardiac arrhythmias, does not reasonably provide enablement "preventing" cardiac arrhythmias. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when

assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdAPIs 1986) at 547 the court recited eight factors:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The instant invention pertains to a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue. The composition comprises a site 1 sodium channel blocker, a local anesthetic, a glucocorticoid receptor, and an additional component selected from agents for treating or preventing cardiac arrhythmias.

State of the art: The skilled artisan would view that prevention of cardiac arrhythmias totally, absolutely, or permanently, so as to not even occur is highly **unlikely**. As noted in the Medline Plus Medical Encyclopedia, hypertrophic cardiomyopathy is a condition in which heart muscles become thick (Definition). Hypertropic cardiomyopathy is usually passed down through families (inherited) (Causes, incidence and risk factors). The first symptom of hypertrophic cardiomyopathy among young patients is sudden collapse and possible death. This is caused by very abnormal heart rhythms (arrhythmias). Hypertrophic cardiomyopathy is a major cause of

death in young athletes who seem completely healthy but dies during heavy exercise (Symptoms). According to the treatment plan the goal of treatment is to control symptoms and prevent complications, not prevent the arrhythmias. Medication is given to help the heart contract and relax correctly. Medication will often relieve symptoms so patients do not need more invasive treatment. Some patients with arrhythmias may need anti-arrhythmic medication. If the arrhythmia is due to atrial fibrillation, blood thinners will also be given to reduce the risk of blood clots (Treatment)

Relative skill of those in the art: The relative skill of those in the art is high, typically requiring an advanced professional degree.

Predictability or lack thereof in the art: The skilled artisan would view that treatment to prevent cardiac arrhythmias to be totally, absolutely, or permanently, as highly unpredictable.

Amount of guidance provided by the inventor and existence of working examples: In the instant case, there is a working example provided in the specification as filed showing how to formulate pharmaceutical compositions and 1 working example provides a protocol for a clinical study for the treatment of epilepsy. However, no working examples are provided or teachings as to formulations that will prevent cardiac arrhythmias. On page 19 of the specification, applicant teaches the first steps in "treating" a patient is identifying a patient suffering from a disease state" (lines 15-22). The specification does not teach "prevention".

Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP §2164.

Genetech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague limitations of general ideas that may or may not be workable.

Therefore, in view of the ***Wands*** factors, e.g., the amount of direction or guidance provided, absence of working examples, the state of the art, and the predictability of the art discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation*** to determine if the compositions administered would "prevent" cardiac arrhythmias.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35-36, 39-42, 44-51 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (WO 98/51290) in view of Levin (US 2002/00101094) and Taylor et al. (US 6,133, 299).

Applicant's Invention

Applicant claims a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue comprising a site 1 sodium channel blocker, a local anesthetic, a glucocorticoid receptor agonist, and an additional component selected from anti-epileptic drugs. Applicant claims the amount of the combination of the components in the composition is effective to treat epilepsy, cardiac arrhythmias or preterm labor. The electrically excitable tissue includes brain, heart, and uterine tissue.

Determination of the scope of the content of the prior art (MPEP 2141.01)

Kohane et al. disclose combinations of naturally occurring site 1 sodium channel blockers such as tetrodotoxin (TTX) (tetrodotoxin, instant invention), saxitoxin, decarbamoyl saxitoxin and neosaxitoxin with other agents to give long duration block with improved features, including safety and specificity (page 3, lines 10-14). Kohane et al. disclose in one embodiment, duration of block is greatly prolonged by combining a toxin with a local anesthetic and glucocorticoid (page 3, lines 15-16)(site 1, sodium channel blocker, tetrodotoxin, local anesthetic and glucocorticoid, instant invention). Kohane et al. further disclose that bupivacaine is the preferred local anesthetic (page 11, lines 22-27) (bupivacaine, instant invention). Kohane et al. disclose corticosteroids that are useful to prolong in vivo nerve blockade include glucocorticoids such as

dexamethasone (page 13, lines 2-3) (dexamethasone, instant invention). Kohane et al. further disclose in example 5, page 35, lines 1-21, the combination of tetrodotoxin with bupivacaine and epinephrine with 0.2% dexamethasone (tetrodotoxin, bupivacaine and dexamethasone in combination, instant invention). Kohane et al. disclose the combination of tetrodotoxin with bupivacaine provides blockade with durations of about 10 hours and the addition of dexamethasone can produce blockade in excess of 30 hours (page 35, lines 13-15). Kohane et al. teach in example 9, page 38, lines 1-13, the effect of the addition of dexamethasone to TTX and bupivacaine containing microspheres. Kohane et al. teach that TTX (0.2% theoretical loading) was combined with 50% by weight bupivacaine and 0.05% dexamethasone in poly(lactic acid-glycolic acid) microspheres. Kohane et al. further teach the average duration of effective block was 7 days. Kohane et al. teach this represents a great improvement over bupivacaine-dexamethasone microspheres, which typically last 3 to 5 days.

Kohane et al. disclose that site 1 toxins do not produce the cardiac or convulsive systemic toxicities of existing local anesthetics. Kohane et al. further teach that combinations of site 1 toxins afford a way of providing prolonged nerve block with better sensory selectivity, markedly reduced risk of convulsions and arrhythmias and extremely high potency on a mass basis (page 7, lines 23-29).

Kohane et al. disclose local anesthetic is preferably delivered to the patient incorporated into a polymer in the form of microparticles, most preferably microspheres (page 14, lines 20-22). Kohane et al. further disclose other forms of the polymers include microcapsules, microencapsulated microspheres, slabs, beads, and pellets,

which in some cases can also be formulated into a paste or suspension (pellets, instant invention) (page 14, lines 22-24). Kohane et al. disclose the anesthetic can be incorporated into the microsphere in a percent loading of 0.1% to 90% by weight, preferably 5% to 75% by weight (page 14, lines 8-10). Kohane et al. disclose the microspheres have a diameter of between approximately 10 and 200 microns, more preferably between 20 and 120 microns (col. 9, lines 60-62) (diameter less than 1 mm, 500 microns, 250 microns and 100 microns, instant invention).

Applicant defines an "effective amount" of an active agent or the microparticles as the amount necessary to elicit the desired biological response. Applicant further discloses that it will be appreciated by those of ordinary skill in this art; the effective amount of microparticles may vary depending on various factors (page 6, lines 21-23-page 7, lines 1-8). Applicant discloses the active agent may be present in the microparticle between 0.0001% and 10% (page 11, lines 19-21). Applicant further discloses that in other embodiments, the active agent may be present in the particle in excess of 90%. Applicant discloses that it would be appreciated by one of skill in the art that the composition of the microparticles will depend on the time-release schedule desired in the particular application. As noted, Kohane et al. teaches that anesthetic, an active agent, can be incorporated into a microsphere in a percent loading of 0.1% to 90% by weight, which falls within the same range of active agents in microspheres disclosed by Applicant. In addition, Kohane et al. teach that TTX (0.2% theoretical loading) was combined with 50% by weight bupivacaine and 0.05% dexamethasone in poly(lactic acid-glycolic acid) microspheres. It is noted that this composition is the

elected invention and the amount of each active agent used in the composition fall within the ranges of what is considered an effective amount as disclosed in Applicant's specification. Therefore, it is duly noted that the composition, site 1 sodium channel blocker, a local anesthetic, and a glucocorticoid receptor agonist, of the prior art is the same as Applicant's composition. Thus, the skilled artisan would recognize that a composition is inseparable from its properties. Hence, all of the properties associated with Applicant's composition would also be possessed by the composition of the prior art, including the intended use to treat epilepsy, cardiac arrhythmias or preterm labor.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Kohane et al. do not teach an additional component selected from the group consisting of anti-epileptic drugs or that the electrically excitable tissue is brain tissue. It is for this reason Levin and Taylor et al. are added as secondary references.

Levin teaches pharmaceutical compositions useful for inhibiting a cerebral neurovascular disorder or a muscular headache in a patient (page 6, paragraph 64). Levin teaches that cerebral neurovascular disorders may be selected from the group consisting of cerebravascular spasm, seizure, and a neurovascular headache (page 5, paragraph 59)(brain tissue, instant invention). Levin teaches the long acting anesthetic pharmaceutical composition comprises a pharmaceutically acceptable carrier and at least one local anesthetic ingredient selected from the group consisting of a long-acting local anesthetic, a persistent local anesthetic and a sustained release formulation of a local anesthetic (page 6, paragraph 60). Levin further teaches in claim 5, page 32, the

local anesthetic is bupivacaine (local anesthetic, bupivacaine, instant invention). Levin teaches in an alternate embodiment the long acting local anesthetic pharmaceutical composition further comprises a pharmaceutically active agent such as tetrodotoxin and a glucocorticoid compound (page 6, paragraph 61) (tetrodotoxin, local anesthetic and glucocorticoid receptor agonist).

Taylor et al. teach in claim 1, col. 12, lines 58-61 a method for treating neurodegenerative diseases or disorders which comprises administering to a mammal in need a therapeutically effective amount of a compound selected from ralitoline, phenytoin, lamotrigine, carbamazepine, lidocaine or tetrodotoxin (anti-epileptic drugs). Taylor et al. teach the anticonvulsant compounds prevent irreversible neuronal damage from conditions similar to ischemia. Taylor et al. further teach anticonvulsant compounds that bind to sodium channels or that cause a voltage-dependent block to sodium currents or that modulate ion channels without simply blocking them are also included in the present invention (col. 4, line 59-67).

Finding a prima facie obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kohane et al., Levin, and Taylor et al. and use additional anti-epileptic drugs to produce a pharmaceutical composition that would be effective in treating a disorder that affects brain tissue. As taught by Kohane et al. the combination of tetrodotoxin, bupivacaine and dexamethasone produced a safe, specific, and potent composition for intercostal blockade for thoracic post-therapeutic neuralgia, lumbar

sympathetic blockade and modality-selective blockade for epidural infusion for postoperative pain. This combination is the same as the claimed invention and therefore, in addition to providing a blockade for neuralgia, would treat epilepsy based on its properties. One skilled in the art would have been motivated to add the additional compounds to the formulations because the compounds claimed are known anticonvulsant compounds used to prevent irreversible neuronal damage from conditions similar to ischemia. Thus, in view of *In re Kerkhoven, 205 USPQ 1069 (C.C.P.A. 1980)*, it is *prima facie* obvious to combine two or more compositions each of which is taught by prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art, thus claims that requires no more than mixing together two or three conventional herbicides set forth prima facie obvious subject matter.

It is also known in the art that nerve tissue is electrically excitable tissue. Levin teaches that a local anesthetic composition alone or in combination with tetrodotoxin or a glucocorticoid compound is effective in treating cerebral neurovascular disorders. Thus, as the compositions safely and effectively treat disorders of electrically excitable tissues, one skilled in the art at the time of invention would have been motivated to combine the teachings.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

Claims 35-36, 39-42, 44-51 and 57-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (WO 98/51290) in view of Webb et al. (US 2001/002404), Bell et al. (US 5,756,497), Levy et al. (US 5,387,419) and Fauza Publication.

Applicant's Invention

Applicant claims a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue comprising a site 1 sodium channel blocker, a local anesthetic and a glucocorticoid receptor agonist and additional component selected from tocolytic agents and agents for treating cardiac arrhythmias. Applicant claims the amount of the combination of the components in the composition is effective to treat epilepsy, cardiac arrhythmias or preterm labor. The electrically excitable tissue includes brain, heart, and uterine tissue

Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Kohane et al. are incorporated herein by reference and are therefore applied in the instant rejection as discussed above.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Kohane et al. do not teach an additional component selected from the group consisting of tocolytic agents or agents for treating cardiac arrhythmias or that the electrically excitable tissue is heart and uterine tissue. It is for this reason Webb, Bell et al., Levy et al., and the Fauza Publication are added as secondary references.

Webb et al. teach that conjugates of pharmaceutical agents and a highly lipophilic group, a C8-C26, naturally occurring unbranched carbon chain, have a different selectivity relative to the unconjugated pharmaceutical agents (page 2, paragraph 19). Webb et al. teach in one embodiment, the conjugates render the activity of these conjugates selective for colon tissue, breast tissue and central nervous system tissue (page 2, paragraph 20) (claim 36, brain tissue (nervous system), instant invention). Webb et al. teach that a method is provided for targeting a therapeutic agent to noncentral nervous system tissue to treat a noncentral nervous system condition (page 2, paragraph 21). Webb et al. further teach the noncentral nervous system tissue can be tissue from the cardiovascular system including heart and vascular system (claim 37, heart tissue, instant invention) and reproductive system including uterus (claim 38, uterine tissue, instant invention) (page 2, paragraph 21-page 3 paragraph 21). Webb et al. teach that the pharmaceutical agent may be any pharmacological compound or diagnostic agent (page 3, paragraph 24). Webb et al. further teach that anesthetic agents include bupivacaine (page 12, paragraph 105)(claim 40, local anesthetic, bupivacaine, instant invention). Webb et al. also teach that glucocorticoid agents include dexamethasone (page 21, paragraph 212) (claims 41-42, glucocorticoid receptor, dexamethasone).

Bell et al. teach the use of benzoxazinone compounds and derivatives and their use as oxytocin receptor antagonists. One application of these compounds is in the treatment of preterm labor in mammals, especially humans. The ability of the compounds to relax uterine contractions in mammals also makes them useful for

treating dysmenorrhea and stopping labor prior to cesarean delivery (Abstract). Bell et al. further teach combinations of the compounds with one or more agents useful in the treatment of disorders such as preterm labor, dysmenorrhea and stopping labor prior to cesarean delivery. More specifically, the compounds may be effectively administered in combination with effective amounts of other tocolytic agents (tocolytic agents) used in the treatment of preterm labor such as β-adrenergic agonists (e.g., ritodrine, isoproterenol, terbutaline, albuterol), magnesium sulfate, ethanol, calcium transport blockers (e.g., nicardipine, nifedipine), and prostaglandin synthesis inhibitors (e.g., indomethacin) (specific tocolytic agents, claim 57). Bell et al. teach the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Bell et al. teach the compounds may also be used in combination with antenatal steroids (e.g., dexamethasone). Bell et al. teach this particular combination has beneficial effects on the neonate by both decreasing uterine activity to prolong gestation and increasing fetal maturation (col. 9, lines 6-35).

Levy et al. teach in the background of the invention, col. 1, lines 34-42, examples of frequently prescribed oral anti-arrhythmic therapeutic agents are digitalis, digitoxin and procainamide. Levy et al. teach other antiarrhythmic agents, such as lidocaine or amiodarone are given intravenously (specific agents for treating cardiac arrhythmias, claim 58). Levy et al. teach other examples of therapeutic agents that are used to treat cardiac rhythmic disturbances include type 1--Sodium Channel Blockers, lidocaine, procainamide, encainide, flecanide; Type 2--Beta Adrenergic Blockers, propranolol;

Type 3--Prolongers of the Action Potential Duration, amiodarone; and Type 4--Calcium Channel Blockers, verapamil, diltiazem, and nickel chloride (specific agents for treating cardiac arrhythmias).

Fauza et al. teach prolonged local blockade of the myometrium with bupivacaine inhibits preterm labor after fetal surgery in rabbits (Abstract). Fauza et al. further teach dexamethasone co-incorporated into bupivacaine-polymer microspheres prolongs sensory and motor block from 8 to 13 fold relative to bupivacaine-polymer microspheres without dexamethasone (page 542, col. 2, paragraph 2).

Finding a prima facie obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kohane et al., Webb et al., Bell et al., Levy et al. and the Fauza Publication and use additional tocolytic agents and agents for treating cardiac arrhythmias that would be effective in treating a disorder that affects heart and uterine tissue. As taught by Kohane et al., the combination of tetrodotoxin, bupivacaine and dexamethasone produced a safe, specific, and potent composition for intercostal blockade for thoracic post-therapeutic neuralgia, lumbar sympathetic blockade and modality-selective blockade for epidural infusion for postoperative pain. This combination is the same as the claimed invention and therefore, in addition to providing a blockade for neuralgia, would treat pre-term labor and cardiac arrhythmias.

One skilled in the art at the time the invention was made would have been motivated to use the composition to treat disorders that affect heart and uterine tissue

because Webb et al. teach that the combination of a pharmaceutical agent with a fatty acid provides a method for selectively targeting pharmaceutical agents to desired tissues. Webb further teaches agents claimed in the instant invention as agents that are used in the compositions for treating preterm labor and cardiac arrhythmias. One skilled in the art would have been further motivated because Webb, Bell et al. and Fauza et al. each teach the use of the claimed tocolytic agents used in combination to treat preterm labor. In addition, Webb et al. and Levy et al. each teach the use of agents to treat cardiac arrhythmias in combinations. In view of *In re Kerkhoven, 205 USPQ 1069 (C.C.P.A. 1980)*, it is *prima facie* obvious to combine two or more compositions each of which is taught by prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art, thus claims that requires no more than mixing together two or three conventional herbicides set forth prima facie obvious subject matter.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

Claims 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Kohane et al. (WO 98/51290) in view of Levin (US 2002/00101094), Taylor et al. (US 6,133, 299) and ten Cate (US 6,352,683).

Applicant's Invention

Applicant claims a pharmaceutical composition for suppressing electrical activity in an electrically excitable tissue comprising a site 1 sodium channel blocker, a local anesthetic and a glucocorticoid receptor agonist and additional component selected from anti-epileptic drugs, tocolytic agents, and agents for treating cardiac arrhythmias. Applicant claims the amount of the combination of the components in the composition is effective to treat epilepsy, cardiac arrhythmias or preterm labor that is provided in a microparticle. Applicant further claims the composition comprises a targeting agent and that the microparticles are triggered to release the agent.

Determination of the scope of the content of the prior art (MPEP 2141.01)

The teachings of Kohane et al., Levin, and Taylor et al. have been discussed earlier in this Office action and the discussion there is incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Kohane et al. do not expressly teach the addition of a targeting agent of claim 52 or that the microparticle is triggered to release by radio-frequency, beams or any of the other methods stated in claim 54. It is for this reason ten Cate is added as a secondary reference.

ten Cate teaches a local and site-specific drug delivery system for delivering a drug to a specific site (col. 2, lines 42-43). ten Cate teaches the drug delivery system is characterized by the combination of a) a carrier material which reflects, absorbs, or emits electromagnetic or mechanical vibrations enabling the monitoring of the material,

b) a drug associated with the carrier material and c) local-delivery means for delivering the carrier material and the drug to the specific site (col. 2, lines 44-50) ten Cate teaches the drug delivery system may also include means for inducing release of the drug from the carrier material when the carrier material is at the specific site, such as means for generating electromagnetic or mechanical vibrations(col. 2, lines 55-59) (triggers, magnetism, instant invention).

ten Cate teaches the carrier material may comprise an ultrasonic contrast agent in the form of microparticles, microbubbles, microspheres, or microcapsules (col. 2, lines 60-62). ten Cate teaches the local-delivery means may comprise a targeting agent associated with the carrier material. ten Cate further teaches the targeting agent is capable of binding to the specific site within the individual (col. 2, lines 65-67-col. 3, line 1). ten Cate teaches the targeting agent may be a protein or an antibody (col. 3, lines 1-5) (antibodies, proteins, instant invention). ten Cate teaches the drug used in the composition may include dexamethasone (col. 3, lines 11-20).

ten Cate teaches the local and site specific drug delivery system is intended to be a system which is capable of transferring or carrying a drug to a specific area or site, at which the system releases the drug in an active or controlled manner enabling the interaction of the drug with the specific area or site, prior to or after administration of the drug delivery system to the human (col. 4, lines 60-67).

Finding a prima facie obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one skilled in the art at the time of the invention to combine the teachings of Kohane et al. Levin, Taylor et al., and ten Cate and use a targeting agent in the composition. As taught by Kohane et al., the combination of tetrodotoxin, bupivacaine and dexamethasone in microspheres produces a longer block than the combination without microspheres (5 to 20 days), which is useful for chronic pain and cancer pain.

One skilled in the art at the time the invention was made would have been motivated to add the targeting agent to provide drug delivery to specific areas or sites that need treatment, as ten Cate teaches targeting agents do. Given the state of the art as evidenced by the teachings of the cited references, and absent any evidence to the contrary, there would have been a reasonable expectation of success in combining the teachings of the cited references to provide a micoparticle composition that targets the specific area or site that needs treatment and that provides prolonged nerve block with better sensory selectivity, markedly reduced risk of convulsions and arrhythmias and extremely high potency on a mass basis.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andriae M. Holt whose telephone number is (571)272-9328. The examiner can normally be reached on 7:00 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richter Johann can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Andriae M. Holt
Patent Examiner
Art Unit 1616

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616